Scientific Abstract

This Phase 2a multicenter, randomized, single-blind, placebo-controlled, dose-escalating safety and efficacy study will evaluate the effects of several dose levels of intramyocardial pVGI.1(VEGF2) plasmid deoxyribonucleic acid (DNA) delivered by percutaneous cardiac catheterization in patients with refractory and stable exertional angina. The pVGI.1(VEGF2) plasmid contains the complementary DNA sequence for the vascular endothelial growth factor 2 protein, a member of a class of natural growth factors that promote angiogenesis. This study will obtain information regarding the safety and effect of this gene for the potential relief of angina.

The primary objectives of this study in adult patients with refractory and stable exertional angina are as follows:

- To assess the safety of single, defined increasing doses of pVGI.1(VEGF2) given by intramyocardial injection using percutaneous cardiac catheterization versus placebo as determined by frequency, severity, and duration of treatment-emergent adverse effects

- To assess the effects of single, defined increasing doses of pVGI.1(VEGF2) given by intramyocardial injection using percutaneous cardiac catheterization versus placebo on change in angina class and exercise tolerance at 12 weeks when compared with pretreatment assessments

A secondary objective of the study is to correlate the changes in angina class and exercise tolerance with changes in myocardial perfusion assessed by myocardial scintigraphy.

The study will consist of a Pretreatment Phase (up to 4 weeks), a Treatment Phase (1 day), a Post-treatment Phase (12 weeks), and a Follow-up Phase (visits at 6 months and 12 months after treatment). This study will include 30 patients who will be enrolled sequentially into 3 dosing cohorts. Each cohort will consist of 10 patients. Within each dosing cohort, patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized to receive either pVGI.1(VEGF2) or placebo in a 1:1 ratio. Within each cohort, treatment of subsequent patients will proceed only after the Week-1 safety data has been reviewed for the previous patient. Dosing in successive cohorts will occur only after the preceding cohort has been completed and the last patient in the preceding cohort has been evaluated for safety for at least 1 week following

completion of the Treatment Phase.

The drug product is an injectable form of plasmid DNA prepared from bulk pVGI.1(VEGF2). Bulk pVGI.1(VEGF2) contains approximately 1 mg plasmid DNA per milliliter in phosphate-buffered saline (20 mM, pH 7.2, containing 0.01% [w/v] edetate disodium). Three pVGI.1(VEGF2) dose levels will be used: 200, 800, and 2000 μg. The appropriate amount of drug substance will be added to Sodium Chloride Injection USP (0.9%) to give a total volume of 6 mL. Each patient will receive the total dose by 6 injections into the ischemic regions of the myocardium using a catheter advanced percutaneously into the left ventricle. Patients randomized to placebo will undergo percutaneous cardiac catheterization but no injections will be performed.

During the Post-treatment Phase, safety will be evaluated based on the adverse experience profile of the patients and on changes in laboratory values, vital signs, and results of physical examination and funduscopy. The effectiveness of treatment will be evaluated by assessing angina class, exercise tolerance, and perfusion defects using myocardial scintigraphy performed with SPECT (using the same protocol and isotope used at baseline) at 12 weeks after treatment as compared with baseline assessment results.

After assessments have been completed at Week 12 of the Post-treatment Phase, patients who received pVGI.1(VEGF2) will enter the Follow-up Phase with visits at 6 months and 12 months after treatment. Patients initially randomized to placebo will repeat the Treatment Phase of this study and will receive active treatment with pVGI.1(VEGF2) at the dose level corresponding to the dose cohort to which they were enrolled. These patients will repeat the Post-treatment Phase of this study and then enter the Follow-up Phase.